

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 7 of 14

claims 16-38 which raise no issue of new matter. New claims 16-37 correspond to previously pending claims 1, 2 and 4-15. In addition, support for new claims 16-37 can be found throughout the specification, for example, *inter alia*, on page 6, lines 14-29, page 10, lines 11-15, page 10, lines 16-30, page 8, lines 25-29, pages 25-26, and pages 35-41.

Drawings

The Examiner has required that new drawings be submitted. In reply, applicant attaches hereto as **Exhibit A** new drawing sheets 1-6, which address the objections identified in PTO-948 (Paper No. 7). Thus, applicant requests the Examiner to withdraw this ground of objection.

Claim for Priority Under 37 C.F.R. §1.55

Applicant submits herewith as **Exhibit B** a new Declaration and Power of Attorney indicating that the subject application claims priority of PCT International Application No. PCT/US97/12239, filed July 9, 1997 and U.S. Serial No. 08/677,112, filed July 9, 1996. Applicant notes that 37 C.F.R. §1.55(a)(1)(ii) indicates that a national stage application must make a priority claim during pendency of the application and within the time limit set forth in the PCT. Applicant notes that PCT Application No. PCT/US97/12239 *did* claim priority of U.S. Serial No. 08/677,112, however the '112 application was not listed on the Declaration filed with the USPTO in connection with the subject national stage application. The new Declaration submitted herewith as **Exhibit B** does list the '112 application. Applicant has also amended the

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 8 of 14

specification to include the claim to this priority. Accordingly, applicant requests that the Examiner acknowledge that the effective filing date of the subject application is July 9, 1996.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1, 2 and 4-15 as not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention.

In reply, Applicant respectfully traverses this rejection and maintains that the claimed invention is fully enabled by the combination of what one of skill in the art would have known at the time of filing of the application and the teachings of the subject specification. The claimed invention is directed to a method for producing a mutagenized polynucleotide encoding a polypeptide having a desired property comprising: blocking or interrupting a polynucleotide synthesis process by contacting a polynucleotide encoding a polypeptide or regulating expression of a polypeptide, with one or more agents that block or interrupt synthesis of the polynucleotide, wherein the agent is selected from UV light, one or more DNA adducts, DNA intercalating agents, DNA binding proteins, triple helix forming agents, competing transcription polymerase, cold or heat, chain terminators, polymerase inhibitors and poisons, and subjecting said polynucleotides to denaturation, hybridization, extension and selection to produce a mutagenized polynucleotide encoding a polypeptide having the desired property.

In response to the Examiner's position regarding required experimentation, applicant points out that in order to practice the claimed invention, one need only to how to test for and select the activity associated with the "desired property." As of the effective filing date, one of

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 9 of 14

skill in the art would have been aware of vast numbers of assays and tests which would be ways to select for such a desired property. The Examiner may have misapprehended the claimed invention, and applicant directs the Examiner's attention to the newly presented claims 16-38. The Examiner states that the claimed invention requires "predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity..." (see page 3 of the February 13, 2002 Office Action). The claimed invention does not require that one practicing it know the sequences of the polynucleotides involved. In addition, there is no need to understand the "detailed...ways in which the protein's structure relates to its function." (See last paragraph of page 3 of the February 13, 2002 Office Action.) The polynucleotide synthesis can be blocked with an agent without knowing the sequence of the polynucleotide and the resultant polynucleotides can be amplified and selected based upon a desired property.

The Examiner also stated that it "not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein." See sentence spanning pages 4-5 of February 13, 2002 Office Action. Applicant respectfully traverses the Examiner's position and asserts that this "screen for multiple substitutions..." is required by the claimed invention. On the contrary, the claimed invention is directed to "blocking or interrupting a polynucleotide synthesis process" and then "subjecting said polynucleotides to denaturation, hybridization, extension and selection to produce a mutagenized polynucleotide encoding a polypeptide having the desired property." It is not necessary to be aware of the specific amino acid substitutions which may occur due to the interrupted synthesis. The predicate laid out by

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 10 of 14

the Examiner is not applicable to the presently pending claims and applicant asserts that the rejection is misapplied.

Furthermore, the Examiner states that the "specification does not support the broad scope of the claims that encompass all modifications and fragments because the specification does not disclose..." a) amino acid sequence for all proteins, nor nucleotide sequence for all proteins; b) general tolerance to modification and the extent of such tolerance; c) specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; d) which fragments, if any, can be made which retain the biological activity of any intact protein; and e) which of the essentially infinite possible choices is likely to be successful. (*See* page 5 of the February 13, 2002 Office Action.) As stated above, applicant points out the claimed methods do not require that one know the original amino acid sequence and/or polynucleotide sequence, let alone identify specific positions or regions of the sequence which can be predictably modified. Moreover, there is no requirement to know which fragments of the original polynucleotide can be made which retain biological activity. The method is discussed hereinabove and only requires the blocking or interrupting of synthesis of a polynucleotide and the subjection of that polynucleotide to denaturation, hybridization, extension and selection to produce a mutagenized polynucleotide encoding a polypeptide having the desired property. (*See* new claims 16-38 submitted herewith.)

Applicant notes that on page 7 of the February 13, 2002 Office Action, the Examiner stated that the claimed method "does not involve any method steps that would screen [f]or otherwise target the amplification interruption/mutagenizing means to a polypeptide having a desired property." Applicant points out that the desired property is one that is selectable. As of

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 11 of 14

the effective filing date of this application, applicant points out that one of skill in the art would have been aware of a vast number of routine selection procedures for identifying a particular desired property in a polypeptide or polynucleotide. Applicant emphasizes that the claimed invention be enabled by the combination of what was known to one of skill in the art as of the filing date of the application and application itself. Therefore, since one of skill in the art would have been aware of the huge number of routine methods available for selecting polypeptides with a desired property, applicant maintains that the claimed invention is fully enabled. Applicant asserts that a mutagenized polynucleotide encoding a polypeptide having a desired property can be routinely and reproducibly realized by the claimed method. Thus, applicant maintains that the claimed invention is fully enabled.

In view of the above remarks and new claims 16-38, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection and allow these claims to pass to issue.

Rejection Under 35 U.S.C. § 101 -Utility

The Examiner rejected claims 1 and 9 because the claimed invention is allegedly not supported by either a credible and substantial asserted utility or a well-established utility. Claims 1 and 9 have been canceled herein without prejudice, however applicant responds to this ground of rejection as it may apply to the pending claims.

In reply, applicant traverses the rejection. In order to clarify the claimed invention, applicant has amended the claims to recite that the polypeptide has a "desired property." The claimed invention is directed to methods for producing a mutant polynucleotide encoding a

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 12 of 14

polypeptide having a desired property and applicant asserts that the claimed invention supports a credible, substantial and specific utility. The claims include the step of subjecting said polynucleotides to denaturation, hybridization, extension and selection procedure to produce a mutant polynucleotide encoding a polypeptide having a desired property. In addition, the claim includes the step of blocking or interrupting a polynucleotide synthesis process by contacting a polynucleotide encoding a polypeptide with one or more agents. Thus, the claimed invention is concerned with polynucleotides involved in the coding or regulation of a gene. Applicant maintains that the claimed invention is supported by a credible, substantial and specific utility, that of producing a mutagenized polynucleotide which encodes a polypeptide with a desired property. The specification provides examples of how the claimed invention is useful. For example, it is useful to increase the combinatorial diversity of an *scfv* library to broaden the repertoire of binding species. *See* page 51 of the application. The specification also teaches that the claimed invention "may be used to generate proteins having altered specificity or activity." The specification states that the claimed invention can be used to generate mutant nucleic acid sequences including promoter sequences or enhancer sequences. The specification goes on to state that the claimed invention can be used to generate genes having increased rates of expression.

Applicant points out that the claimed invention requires a selection (*see* line 9 of claim 1) and that one of skill in the art would have been aware of a vast number of selection assays which could be used in the claimed method. The utility of creating a mutagenized polynucleotide which expresses a polypeptide having a desired property is credible, substantial and specific. In

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 13 of 14

view of the amendments and remarks made herein, applicant requests that the Examiner reconsider and withdraw this ground for rejection.

Rejection Under 35 U.S.C. § 102 – Pues et al.

The Examiner rejected claims 2, 6-8 and 10 as being anticipated by Pues et al. In reply, applicant maintains that Pues et al. (March 1997) does not qualify as prior art as to the present application. Applicant has amended the priority claim in the present application. The first sentence of the application is amended herein and a new Declaration of the inventors is submitted herewith as **Exhibit B**, which now expressly includes a claim of priority to the priority U.S. application (U.S. Serial No. 08/677,112, filed 9 July 1996) of PCT International Application No. PCT/US97/12239. The present application is the U.S. national stage application of this PCT. Accordingly, the effective filing date of the subject application is July 9, 1996 and therefore, Pues et al. (March 1997), does not qualify as prior art under 35 U.S.C. § 102. Thus, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

Applicant: Jay M. Short
U.S. Serial No.: 09/214,645
Filed: September 27, 1999
Page 14 of 14

Conclusion

Applicant has addressed all of the issues raised by the Examiner and requests reconsideration and withdrawal of the outstanding rejections. In addition, applicant requests an interview with the Examiner via telephone prior to the issuance of the next action.

The Commissioner is hereby authorized to debit any fee, other than an issue fee, that may be required from Deposit Account No. 08-0219. If there are any questions concerning this application, the Examiner is invited to call the undersigned at her telephone number indicated below.

Respectfully submitted,

Date: August 13, 2002

Jane M. Love
Jane M. Love, Ph.D.
Reg. No. 42,812
Attorney for Applicant

HALE AND DORR LLP
300 Park Avenue
New York, New York 10022
Tel.: (212) 937-7233 (direct)
Fax: (212) 937-7300
jane.love@haledorr.com